

Remarks

Applicants request consideration on the merits of the above-referenced patent application.

I. Amendments to the specification

Various citations on pages 4, 6, 871, and 880 have been amended. Applicants submit that these amendments correct obvious errors, and are therefore permissible under MPEP §2163.07. Applicants further submit that these amendments are supported by the cited references themselves.

The specification inadvertently uses “Y” to identify two different variables. Specifically, the specification uses “Y” to describe a portion of the X-Y-Z ring between the carbonyl and sulfonyl of Applicants’ compounds. The specification also uses “Y” to describe the terminal end of the sulfonyl substituent (*i.e.*, -G-A-R-E-Y). Applicants have amended the specification to change the “Y” in the -G-A-R-E-Y substituent to “Y²” to reflect the fact that it is different from the “Y” of the X-Y-Z ring structure between the sulfonyl and carbonyl. Applicants have made this amendment at:

- Formula II at line 4 on page 15;
- the paragraph bridging pages 20 and 21;
- the paragraph bridging lines 23-24 on page 22;
- the paragraph bridging pages 22 and 23;
- the paragraph bridging lines 20-23 on page 23;
- the paragraph bridging lines 3-6 on page 25;
- the paragraph bridging lines 4-11 on page 27;
- Formula II at line 19, page 42;
- the paragraph bridging lines 7-13 on page 48;
- the paragraph bridging lines 4-5 on page 50;
- the paragraph bridging lines 6-21 on page 50;
- the paragraph bridging pages 50 and 51;
- the paragraph bridging line 9-13 on page 58;
- the paragraph bridging pages 76 and 77;
- the paragraph bridging lines 7-24 on page 77;

the paragraph bridging lines 1-8 on page 78;
the paragraph bridging pages 95 and 96;
Scheme C at line 17 on page 103 (structure no. 3);
the paragraph bridging lines 13-18 on page 104; and
the paragraph bridging lines 19-31 on page 104.

These amendments correct an obvious error, and are therefore permissible under MPEP §2163.07. They also are supported by Applicants' specification at, for example, claims 7, 52, and 105-106 (as originally filed); page 16, line 1 to page 17, line 4; and page 20, line 26 to page 23, line 10. Specifically, this text defines Y differently, depending on whether it is a part of the G-A-R-E-Y substituent or part of the X-Y-Z ring structure between the carbonyl and sulfonyl.

Applicants also have amended the chemical structures in Schemes B and C on pages 101 and 103 to include two bonds between the sulfur and oxygen(s). These amendments correct an obvious error, and are therefore permissible under MPEP §2163.07. In addition, they are supported by Applicants' specification at, for example, page 95, lines 6-11; page 99, lines 10-16; and page 100, lines 3-8. Specifically, this text points out the fact that the schemes illustrate that the sulfur in the structures may be part of a thio, sulfoxide (which is -S(=O)-), or sulfone (which is -S(=O)₂-).

Other amendments simply rephrase the specification, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

II. Amendments to claims

This Amendment D adds claims 162-164. Thus, claims 7-16, 20-22, 26-28, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-164 are pending. It should be noted the Office action did not cite claims 26-28 as being canceled or pending. Applicants request that the Examiner expressly recognize that claims 26-28 are pending.

This Amendment D amends claims 7, 8, 10, 14, 15, 20, 21, 35, 52, 53, 55, 59, 62, 69, 82-84, 147, 148, and 157-159. The claims, including the amendments, are shown in the previous section. Applicants submit that the amendments do not introduce new matter. Specifically:

Method-of-treatment claims 7, 15, 20, and 35 have been amended to characterize the target condition as a condition that is treatable by inhibiting matrix metalloprotease activity.

This amendment is supported by Applicants' specification at, for example, claims 7, 15, 20, and 35 (as originally filed); and page 1, lines 7-13. Claims 7, 15, 20, and 35 also have been amended to replace their compound definitions with references to the compound definitions in compound claims 52, 62, 158, and 87, respectively.

The structures and substituent definitions in claims 8, 10, 14, 52, 53, 55, 59, 147, and 148 have been amended to change the "Y" in the G-A-R-E-Y substituent to "Y²" to reflect the fact that it is different from the "Y" of the X-Y-Z ring structure between the sulfonyl and carbonyl. As with the analogous amendments to the specification, these claim amendments correct an obvious error, and are therefore permissible under MPEP §2163.07. They also are supported by Applicants' specification at, for example, claims 7, 52, and 105-106 (as originally filed); page 16, line 1 to page 17, line 4; and page 20, line 26 to page 23, line 10.

The R⁸, R⁹, R¹⁰, and R¹¹ definitions in claims 52, 62, and 158 have been amended to more clearly recite the sulfone and sulfoxide substituents. The R³ definition in claim 158 has been amended in a similar manner.

The "R" definition in claim 52 has been amended to remove alkyl and alkoxyalkyl. Following this amendment, the "R" moiety comprises at least one ring structure. This amendment renders redundant the language in the G-A-R-E-Y² definition characterizing the G-A-R-E-Y² substituent as comprising two ring structures. Thus, that language has been removed.

The structures in claims 157 and 159 have been amended to make the sulfonyl substituents consistent with the claims from which claims 157 and 159 depend (*i.e.*, claims 20 and 158, respectively).

Other amendments correct grammatical and/or obvious errors, or simply rephrase the claims. These amendments are permissible under MPEP §2163.07.

New claim 162 is analogous to claim 52 as amended by Amendment B, except formula II and the R⁸, R⁹, R¹⁰, and R¹¹ definitions incorporate the amendments described above for claim 52; the "Y" of the G-A-R-E-Y moiety is identified as "Y²"; the G-A-R-E-Y² definition does not include the language characterizing the G-A-R-E-Y² substituent as comprising two ring structures; and the Y² definition does not include hydrido, alkyl, alkoxy, haloalkyl, hydroxy, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl.

New claim 163 is directed to methods of treatment using the compounds and salts of claim 162.

And new claim 164 is directed to pharmaceutical compositions comprising the compounds and salts of claim 162.

III. Response to rejection of under 35 USC. §112 in Paragraph 2

Claims 7, 15, 20, 52, 62, and 156 have been rejected under 35 USC §112 (second paragraph) for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, these claims have been rejected because various substituents definitions include Markush group that recites the phrase "a sulfoxide of any of said thio substituents, a sulfone of any of said thio substituents." Applicants note that claim 156 does not include the phrase at issue. Claim 158, however, does include the phrase. Thus, Applicants assume that the Examiner meant to reject claim 158 rather than claim 156.

Applicants request withdrawal of this rejection. Applicants submit that the phrase is proper --- it simply indicates that the Markush group includes the sulfinyl and sulfonyl derivatives of any thio-containing substituent listed in the Markush group. Nevertheless, the amendments in this Amendment D have obviated this rejection. Specifically, the amendments have removed the phrase from claims 7, 15, and 20. And, in claims 52, 62, and 158, the amendments have replaced the phrase with the specific substituents to which the phrase referred. Applicants note that these amendments simply rephrase the claims, and are not intended to affect the scope of the claims.

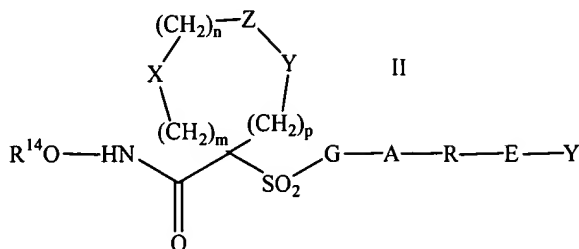
IV. Obviousness rejections in view of Bender and/or Venkatesan in Paragraph 3

Claims 7-16, 20-22, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-161 have been rejected under 35 USC. §103 in view of Bender et al. (U.S. Patent No. 5,932,595), Venkatesan et al. (International Publication No. WO 98/37877), or Venkatesan et al. in view of Bender et al. Applicants request reconsideration of this rejection.

Claim 7

Claim 7 is directed to the use of a compound (or salt thereof) to treat a mammal having a

condition associated with pathological MMP activity. The compound corresponds in structure to formula II:



As amended by this Amendment D, claim 7 recites compounds wherein the G moiety and the R moiety each comprise a ring structure. Thus, the compounds of amended claim 7 have the following structural combination: (1) one carbon atom separating the carbonyl from the sulfonyl, and (2) a sulfonyl substituent (*i.e.*, -G-A-R-E-Y) that comprises at least two ring-containing moieties (*i.e.*, G and R). As the Examiner acknowledged during the below-identified calls with the Undersigned, the cited references (whether viewed alone or together) fail to teach or suggest such a combination.

More specifically, Bender et al. disclose compounds with two carbon atoms separating the carbonyl from the sulfonyl (*i.e.*, “2-carbon compounds”). Bender et al. fail to teach, suggest, or provide motivation for compounds or salts having one carbon atom separating the carbonyl from the sulfonyl. Thus, the compounds of amended claim 7 are patentable over Bender et al.

Venkatesan et al. disclose compounds with a single-ring substituent on the sulfonyl. Venkatesan et al. fail to teach, suggest, or provide motivation for compounds with a multi-ring substituent on the sulfonyl. Thus, the compounds of amended claim 7 are patentable over Venkatesan et al.

The cited references fail to teach, suggest, or provide motivation for combining their teachings. As noted in MPEP §2143.01:

the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

Here, neither reference provides any express motivation to combine their teachings. And there is no implied motivation to combine their teachings either. To the contrary, the cited references are focused on structurally different compounds.

Even if viewed together, the cited references fail to teach, suggest, or provide motivation

and enablement for all the elements of claim 7. As noted in MPEP §706.02(j), prior art references can only support a *prima facie* showing of obviousness if they teach or suggest all the claim limitations. Here, the cited references (even if viewed together) fail to teach, suggest, or provide motivation for compounds with (1) one carbon atom separating the carbonyl from the sulfonyl, and (2) a multi-ring substituent on the sulfonyl. And, even if such motivation did exist in the art, the cited references would not have enabled one skilled in the art to predict how the compound substituents could be altered to achieve the compounds recited in claim 7. *See* MPEP §2121.02 (prior art must be enabling to support a rejection). Thus, the compounds of amended claim 7 are patentable over Venkatesan et al. in view of Bender et al.

Claims 8-16, 20-22, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-161

Like claim 7, claims 8-16, 20-22, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-161 recite compounds that have a structural combination of (1) one carbon atom separating the carbonyl from the sulfonyl, and (2) a sulfonyl substituent that comprises at least two ring-containing moieties. Thus, these claims are patentable over the cited references for the same reasons as stated above with respect to claim 7, and by reason of the additional limitations that claims 8-16, 20-22, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-161 recite.

New claims 162-164

Like claim 7, new claims 162-164 recite compounds that have the structural combination of (1) one carbon atom separating the carbonyl from the sulfonyl, and (2) a sulfonyl substituent that comprises at least two ring-containing moieties (here, at least G and Y comprise a ring structure). Thus, these claims are patentable over the cited references for the same reasons stated above with respect to claim 7, and by reason of the additional limitations that claims 162-164 recite.

V. Double-patenting rejection in Paragraph 4

Claims 7-16, 20-22, 35-42, 52-65, 67-71, 82-85, 87-94, 128-131, and 147-161 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,541,489. Applicants submit that this rejection

is premature because the claims have not yet been found to be otherwise allowable. Applicants will file a terminal disclaimer (to the extent necessary) once the claims have been found to be otherwise allowable. If, as Applicants anticipate, the Examiner finds the claims in this Amendment D to be otherwise allowable, Applicants request that the Examiner call the Undersigned to address this issue.

VI. Calls Between Examiner and Undersigned

The Examiner and Undersigned discussed this application during calls on November 5, 2003; November 6, 2003; November 12, 2003; and December 4, 2003. During those calls, the Examiner and Undersigned clarified the May 8, 2000 restriction requirement. The Examiner and Undersigned also discussed the obviousness rejections based on Bender et al. and Venkatesan et al. (outlined in the May 3, 2001 Office action); the G-A-R-E-Y definition in claims 7 and 52; the R⁸, R⁹, R¹⁰, and R¹¹ definitions in claims 52, 62, and 158; the R³ definition in claim 158; the language of the independent method-of-treatment claims (*i.e.*, claims 7, 15, 20, and 35); and the scope of the claims in U.S. Patent No. 6,541,489. Although no final agreement was reached as to the patentability of the claims, the Examiner indicated that claims (as amended) would be patentable over the cited references.

Applicants and the Undersigned thank the Examiner for her courtesy and preparedness during the telephone calls.

VII. Supplemental Declaration under 37 CFR §1.132

Applicants have enclosed a supplemental declaration from Dr. Joseph J. McDonald under 37 CFR §1.132. That supplemental declaration clarifies Paragraph 5 of Dr. McDonald's November 2, 1001 declaration. The supplemental declaration also discloses additional tetrahydropyranyl compounds prepared by Pharmacia that have a single-ring phenyl substituent on the sulfonyl and MMP-1 and MMP-13 inhibition data for those compounds (to the extent such data is available).

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Applicants have enclosed a check for \$1720.00 to cover the three-month extension and request for continued examination fees. Applicants believe that they do not owe any additional

Amendment D (After Final Rejection)

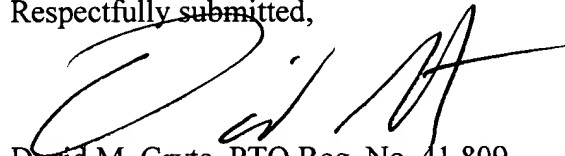
Appl. No. 09/311,837

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fees for this filing. However, if Applicants owe any additional fee(s) in connection with this filing, the Commissioner is hereby authorized to charge those fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

Applicants submit that the pending claims are in condition for allowance, and request that this application be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'D. M. Gryte', is written over the typed name.

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